REMARKS

These remarks are in response to the Office Action mailed September 10, 2003. The specification has been amended to delete the browser-executable hyperlink found in paragraphs 141, 164, and 205. Claims 12, 14, and 23 have been amended to more particularly define Applicants' invention. Thus, the amendments introduce no new matter. Claims 1-24 are pending.

A. Rejections Under 35 U.S.C. § 112, Second Paragraph

The rejection of claims 12, 14, 16-18, and 20-24 under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim subject matter which Applicants regard as the invention, is respectfully traversed.

With specific reference to the phrase "said complex mixture" as used in claims 12 and 14, the rejection is rendered moot since this phrase has been amended to read "said complex mixture of proteins." The Examiner's suggestion of acceptable alternative language is acknowledged with appreciation.

With specific reference to the phrases "said functional group" and "said sulfonyl group" as used in claims 12 and 14, the rejection is rendered moot since these phrases have been amended to each read "said sulfonyl functional group." The Examiner's suggestion of acceptable alternative language is acknowledged with appreciation.

With specific reference to the phrases "said library" and "said combinatorial library" as used in claim 12, the rejection is rendered moot since these phrases have been amended to each read "said combinatorial chemical library." The Examiner's suggestion of acceptable alternative language is acknowledged with appreciation.

With specific reference to the phrases "said active and inactivated complex mixture," "said inactivated complex mixture," and "said active complex mixture" as used

in claim 12, Applicants respectfully disagree with the Examiner's assertion that there is allegedly insufficient antecedent basis for these phrases. Clause (1) in claim 12 recites "combining with said complex mixture of proteins, in an active form and an inactivated form (emphasis added). It is submitted that this clause provides sufficient antecedent basis for subsequent recitation in claim 12 of the phrases in question.

With specific reference to the phrase "active form and inactivated form" as used in claim 12, it is respectfully submitted that there is no ambiguity associated with this phrase. When considering claim 12 in view of the specification, those skilled in the art readily recognize that "active form and inactivated form" refers to the complex mixture of proteins, and not the chemical library. Indeed, it is clear that the members of the chemical library are used to screen for molecules that can distinguish active proteins from inactive proteins in a complex mixture of proteins.

With specific reference to the phrase "the total target protein" as used in claim 14, the rejection is rendered moot since this phrase no longer appears in claim 14.

With specific reference to the phrase "said second portion of said complex proteomic mixture" as used in claim 23, the rejection is rendered moot since this phrase no longer appears in claim 23.

For all of the reasons set forth above, it is respectfully submitted that the rejections of claims 12, 14, 16-18, and 20-24 under 35 U.S.C. § 112, second paragraph, are not properly applied. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

B. Rejection Under 35 U.S.C. § 112, First Paragraph (Written Description)

The rejection of claims 12, 14, 16-18, and 20-24 under 35 U.S.C. § 112, first paragraph, as containing subject matter which allegedly was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention, is respectfully traversed.

The burden of demonstrating that the claims are allegedly not supported by an adequate written description falls on the Examiner. *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976). In this case, the Examiner has provided insufficient evidence to call into question the written description set forth in the present application. Accordingly, for the following reasons, it is respectfully submitted that the Examiner has not met the burden of demonstrating an alleged lack of written description for the claimed invention.

Applicants respectfully disagree with the Examiner's assertion that the specification allegedly contains insufficient written description to support the entire scope of the presently claimed invention. In contrast to the Examiner's assertion, it is respectfully submitted that methods for screening for molecules having an affinity for an active protein in a complex mixture of proteins from a biological source are sufficiently described throughout the specification. For example, at page 10, paragraph 39, the specification describes, as follows,

> The combinatorial chemical libraries of the present invention are useful as screening tools for discovering new lead structures through evaluation of the compounds in the library across an array of biological assays, including the discovery of selective inhibition patterns across isozymes and related enzymes, where the enzymes share a common functionality at the active site, allelic

proteins, binding to a family of ligands, etc. Thus, the library is useful as a tool for drug discovery, i.e., it is a means to discover novel lead compounds by screening the library against a variety of biological targets, and also as a tool for the development of structure-activity relationships in large families of related compounds.

Moreover, at page 17, paragraph 78, the specification reads as follows:

The combinatorial libraries of the present invention may be screened for pharmacologically active compounds, including analogs, that is compounds that can affect the biological status of a biological system, usually a cellular system. The biological system will depend on the use of a biological source that will include cells and/or viruses. By pharmacologically active is meant that a compound may effect the function of a protein, e.g, an enzyme, including physiological process such as signal transduction by a cellular receptor, initiation, cessation or modulation of an immune response, modulation of heart function, nervous system function, or any other organ or organ system. A pharmacologically active compound may also stimulate or inhibit the activity of a bacteria, virus, fungus, or other infectious agent. A pharmacologically active compound may modulate the effects of a disease, that is prevent or decrease the severity of or cure a disease such as cancer, diabetes, atherosclerosis, high blood pressure, Parkinson's disease and other disease states. Screening for pharmacological activity may be performed by assays as would be known in the art, depending on the function or activity to be assessed.

In addition, at page 31, paragraph 112, the specification reads as follows:

In the case of affinity labels, one can determine the available activity in a protein composition of the target proteins, one can differentiate the activity between the target protein and other members of the class on the properties of the protein

composition, e.g. cell(s) or lysate, one can obtain a protein activity profile for tissue, cells or lysate in response to various stimuli and one can screen compounds for their binding affinity to the target protein, e.g. drug screening.

Thus, when claims 12, 14, 16-18, and 20-24 are considered in view of the specification, those skilled in the art readily recognize that the specification contains sufficient written description for methods for screening for molecules having an affinity for an active protein in a complex mixture of proteins from a biological source.

Furthermore, Applicants respectfully disagree with the Examiner's assertion that the rejected claims contain "no distinguishing structural attributes" with respect to the "activity based probes." In response to this assertion, Applicants respectfully direct the Examiner's attention to *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 :

"The written description requirement may be satisfied through sufficient description of a representative number of species..." (emphasis added).

Moreover, it is submitted that an adequate description of a "representative number of species" does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. *In re Bell,* 991 F.2d 781, 785 26 USPQ2d 1529, 1532 (Fed. Cir. 1993) With respect to the active target members set forth in the specification, it is submitted that the specification clearly describes a "representative number of species" to demonstrate that Applicants were in possession of the claimed active target members.

It is well-established that claims are to be interpreted in light of the specification (*AFG Industries, Inc. v. Cardinal IG Co., Inc.,* 239 F.3d 1239, 57 USPQ 2d 1776 (Fed. Cir. 2001) The specification contains more than sufficient guidance with respect to the identifying characteristics of "active target members." For example, at page 16, paragraph 75, the specification describes examples of target proteins, as follows:

> Exemplary protein targets described herein include enzymes, included in the groups oxidoreductases, hydrolases, ligases, isomerases, transferases, and lyases and include such enzymes or enzyme groups as serine hydrolases, metallo-hydrolases, dehydrogenases, e.g. alcohol and aldehyde dehydrogenases, and nucleotide triphosphate (NT)-dependent enzymes, although, the invention envisions ABPs which recognize any protein, e.g., enzyme, family. Other proteins include proteins that bind to each other or to nucleic acids, such as transcription factors, kringle structure containing proteins, nucleic acid binding proteins, G-protein binding receptors, cAMP binding proteins, etc.

Similarly, at page 17, paragraph 76, the specification provides, "Targets of interest will be particularly enzymes, other proteins include receptors, transcription factors, G-proteins, and the like." See also, page 32, paragraph 115, where the specification describes various types of enzymes that may serve as target proteins:

> Enzymes typically fall within six main classes including oxidoreductases, transferases, hydrolases, lyases, isomerases and ligases. In a particular embodiment illustrated herein, an enzyme group of interest includes the class of hydrolases. One genus of the class is serine hydrolases, which includes sub-genera such as proteases, e.g.trypsins, chymotrypsins, esterases, such as acetylcholinesterases, thioesterases, amidases, such as FAAH, and acylpeptide hydrolases, lipases, transacylases, such as lecithin:cholesterol acyltransferase. Another sub-genus is cysteine hydrolases, such as caspases, cathepsins, and palmitoyl acyltransferases. Another sub-genus is metallohydrolases, including matrix metalloproteinases ("MMPs"), e.g. MMP1 – 13, membrane type metalloproteinases, aminopeptidases, and ADAMalysins. In addition, are phosphatases, such as alkaline phosphatases, acid phosphatases, protein tyrosine phosphatases, and serine/threonine phosphatases. Further included are the GTPases and ATPases. Besides hydrolases are kinases, which include enzymes such as tyrosine kinases, e.g. src, abl, and lck, serine/threonine kinases, e.g. MAP

kinases, MAPK kinases, CAM kinases, protein kinase C, and casein kinases. Also of interest are oxidoreductases, such as cytochrome P450s, amine oxidases, alcohol dehydrogenases, aldehyde dehydrogenases, such as ALDH1, ALDH2, ALDH3, desaturases, etc. Other proteins that are of interest include receptors, such as HLA antigens, hormone receptors, G-proteins coupled receptors, ion channels, transcription factors, protein inhibitors and the like.

Additionally, the specification describes what is meant by "related group of proteins," that is, proteins that perform the same activity, and provides examples. See, for example, page 26, paragraph 101:

> The probe may be specific for a single protein or more usually a related group of proteins. By related group of proteins is intended proteins that perform the same activity, as with enzymes that belong to the same group and catalyze the same reaction, e.g. hydrolysis, phosphorylation, oxidation, etc., and usually having one or more of the following characteristics: the same functionality at the active site; the same spatial orientation of functional groups that bind to the ligand; similar spatial structure and conformation; similar molecular weight; the same or similar cofactors or complexing proteins; and similar function. To enhance the distinction between active proteins and inactive proteins, special chemically reactive groups are employed.

Applicants also respectfully disagree with the Examiner's assertion that the specification is allegedly narrow in scope describing only one library of activity based probes (ABPs). Because the ABPs employed in the claimed methods label proteins in an activity-dependent manner, those skilled in the art recognize that each ABP will vary depending upon the target protein(s) chosen for activity-based analysis. It is respectfully submitted that the ability to label proteins in an activity-dependent manner is a readily identifiable characteristic that, combined with the abundant information provided with respect to selection of target proteins and characterization of functional groups of

activity-based probes directed to various target proteins, is sufficient to demonstrate possession of the claimed invention. The specification provides, for example, at page 19, paragraph 82, that "a functional group (F) . . . specifically and covalently bonds to the active site of a protein." The specification also provides examples of particular functional groups, for example, at page 20, paragraph 84:

> Exemplary Fs as used in an ABP of the invention include an alkylating agent, acylating agent, ketone, aldehyde, sulphonate or a phosphorylating agent. Examples of particular Fs include, but are not limited to fluorophosphonyl, fluorophosphoryl, fluorosulfonyl, alpha-haloketones or aldehydes or their ketals or acetals, respectively, alpha-haloacyls, nitriles, sulfonated alkyl or aryl thiols, iodoacetylamide group, maleimides, sulfonyl halides and esters, isocyanates, isothiocyanantes, tetrafluorophenyl esters, N-hydroxysuccinimidyl esters, acid halides, acid anhydrides, unsaturated carbonyls, alkynes, hydroxamates, alpha-halomethylhydroxamates, aziridines, epoxides, or arsenates and their oxides. Sulfonyl groups may include sulfonates, sulfates, sulfinates, sulfamates, etc., in effect, any reactive functionality having a sulfur group bonded to two oxygen atoms. Epoxides may include aliphatic, aralkyl, cycloaliphatic and spiro epoxides, the latter exemplified by fumagillin, which is specific for metalloproteases.

Additionally, the specification provides guidance on the selection of an appropriate functional group for protein target, for example, at page 27, paragraph 102:

> A "chemically reactive group" is a moiety including a reactive functionality that does not react efficiently with the generally available functional groups of proteins, e.g. amino, hydroxy, carboxy, and thiol, but will react with a functionality present in a particular conformation on a surface. In some situations the reactive functionality will serve to distinguish between an active and an inactive protein. In other situations, the conformation of the chemically reactive group will bind to the specific conformation of the target protein(s), whereby with

a slowly reactive functionality or one that requires activation, the predominant reaction will be at the active site. For example a photoactivatable group may be used such as a diazoketone, arylazide, psoralen, arylketone, arylmethylhalide, etc. any of which can bind non-selectively to the target protein, while the probe is bound to the active site. Olefins and acetylenes to which are attached electron withdrawing groups such as a sulfone, carbonyl, or nitro group may be used to couple to sulfhydryl groups.

The specification provides much guidance with respect to the selection of "active target proteins." For example, the specification provides at page 32, paragraph 114:

For many of the enzyme genera, functionalities are known that do not significantly react with enzymes of other genera, particularly non-enzymatic proteins and enzymes that have different reactive sites. It is also desirable that the functionality does not react with inactive target enzyme. Examples of inactive states include: 1) proenzymes, e.g. requiring cleavage of the protein; 2) enzymes bound by endogenous inhibitors (either covalent or non-covalent); 3) enzymes in an inactive conformation (e.g. enzymes that require the binding of another protein, a conformational change, covalent modification by phosphorylation/reduction/oxidation/methylation/acylation (e.g. formic or acetic acid) for conversion to an active state; 4) denatured enzymes; 5) mutant enzymes; 6) enzymes bound by either reversible or irreversible exogenous inhibitors; and 7) enzymes requiring a cofactor for activity. The enzymes of interest will usually have at least one of serine, threonine, cysteine, histidine, lysine, arginine, aspartate or glutamate as a member of the active site involved in the catalysis of the enzyme reaction. One or more of the functionalities of these amino acids may be the target of the ABP. The manner in which the inactive enzyme is inactivated

is chosen to emphasize the differences in bonding of the ABP between the active and inactive state.

Thus, the specification provides adequate guidance for selection of common functionalities.

Applicants also respectfully disagree with the Examiner's assertion that "specification description is directed to the syntheses of a specific probe (e.g., the biotinylated fluorophosphonate probe such as FP-biotin and FP-peg biotin) that have specificity toward an "active target member" (e.g., serine hydrolases). As noted above, the specification clearly sets forth a wide variety of proteins contemplated for use in the practice of the invention and sets forth (for exemplary purposes only) activity-based quantitation and determination of the serine hydrolases (see specification, Example 4). In addition, the specification describes several sulfonate ester activity-based probes (see, for example, Example 7) . Applicants respectfully point out that particular examples of ABPs set forth in the Examples are merely illustrative and not intended to be limiting.

It is respectfully submitted that Applicants are entitled to claims drawn as broadly as the prior art will allow. The activity characteristics set forth in the present claims are the most appropriate descriptions known to Applicants to describe the methods of the present invention. Thus, it is submitted that the specification "clearly allows persons of ordinary skill in the art to recognize that he or she invented what is claimed." *Union Oil Co. of California v. Atlantic Richfield Co.* 54 USPQ2d 1227 (2000)

Applicants submit that the present specification contains a complete description of the invention sufficient to enable a person skilled in the art to utilize the methods of the invention. Accordingly, it is respectfully submitted that the rejection of claims 12, 14, 16-18, and 20-24 under 35 U.S.C. § 112, first paragraph, as allegedly lacking adequate written description, is not properly applied. Reconsideration and withdrawal of the rejection are therefore respectfully requested.

C. Rejection Under 35 U.S.C. § 112, First Paragraph (Enablement)

The rejection of claims 12, 14, 16-18, and 20-24 under 35 U.S.C. § 112, first paragraph, , as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, is respectfully traversed. Applicants respectfully disagree with the Examiner's assertion that the specification allegedly does not teach one skilled in the art how to make and/or use the invention commensurate in scope with the claims.

It is well-established that the claims of a patent application are presumptively enabled when the application is filed. Thus, the burden of demonstrating that the entire breadth and scope of the claims is allegedly not enabled falls on the Examiner. In this case, the Examiner has provided no evidence to call into question the enablement of the claims. Accordingly, for all of the following reasons, it is respectfully submitted that the Examiner has not met the burden of demonstrating non-enablement.

First , Applicants respectfully disagree that the claims include an "infinite number of methods for producing and/or using an infinite number of structural variants (i.e., activity based probes)." In contrast, it is submitted that the specification describes well-defined A activity based probes, such that skilled artisans can readily determine the probes set forth in the claims. For example, the specification provides, for example, at page 19, paragraph 82, that "a functional group (F) . . . specifically and covalently bonds to the active site of a protein." The specification also provides examples of particular functional groups, for example, at page 20, paragraph 84:

> Exemplary Fs as used in an ABP of the invention include an alkylating agent, acylating agent, ketone, aldehyde, sulphonate or a phosphorylating agent. Examples of particular Fs include, but are not limited to fluorophosphonyl, fluorophosphoryl, fluorosulfonyl, alpha-haloketones or aldehydes or their ketals or acetals, respectively, alpha-haloacyls, nitriles, sulfonated alkyl or aryl thiols,

iodoacetylamide group, maleimides, sulfonyl halides and esters, isocyanates, isothiocyanantes, tetrafluorophenyl esters, N-hydroxysuccinimidyl esters, acid halides, acid anhydrides, unsaturated carbonyls, alkynes, hydroxamates, alpha-halomethylhydroxamates, aziridines, epoxides, or arsenates and their oxides. Sulfonyl groups may include sulfonates, sulfates, sulfinates, sulfamates, etc., in effect, any reactive functionality having a sulfur group bonded to two oxygen atoms. Epoxides may include aliphatic, aralkyl, cycloaliphatic and spiro epoxides, the latter exemplified by fumagillin, which is specific for metalloproteases.

Additionally, the specification provides guidance on the selection of an appropriate functional group for protein target, for example, at page 27, paragraph 102:

A "chemically reactive group" is a moiety including a reactive functionality that does not react efficiently with the generally available functional groups of proteins, e.g. amino, hydroxy, carboxy, and thiol, but will react with a functionality present in a particular conformation on a surface. In some situations the reactive functionality will serve to distinguish between an active and an inactive protein. In other situations, the conformation of the chemically reactive group will bind to the specific conformation of the target protein(s), whereby with a slowly reactive functionality or one that requires activation, the predominant reaction will be at the active site. For example a photoactivatable group may be used such as a diazoketone, arylazide, psoralen, arylketone, arylmethylhalide, etc. any of which can bind non-selectively to the target protein, while the probe is bound to the active site. Olefins and acetylenes to which are attached electron withdrawing groups such as a sulfone, carbonyl, or nitro group may be used to couple to sulfhydryl groups.

Furthermore, Applicants respectfully disagree with the Examiner's assertion that the invention is allegedly not applicable to enzymes other than cALDH-I. Indeed, it is submitted that the Examiner provides no evidence to support the assertion that the invention is allegedly not applicable to enzymes other than cALDH-I. In contrast to the Examiner's assertion, the specification provides much guidance with respect to the selection of "active target proteins." For example, the specification provides at page 32, paragraph 114:

> For many of the enzyme genera, functionalities are known that do not significantly react with enzymes of other genera, particularly non-enzymatic proteins and enzymes that have different reactive sites. It is also desirable that the functionality does not react with inactive target enzyme. Examples of inactive states include: 1) proenzymes, e.g. requiring cleavage of the protein; 2) enzymes bound by endogenous inhibitors (either covalent or non-covalent); 3) enzymes in an inactive conformation (e.g. enzymes that require the binding of another protein, a conformational change, covalent modification by phosphorylation/reduction/oxidation/methylation/acylation (e.g. formic or acetic acid) for conversion to an active state; 4) denatured enzymes; 5) mutant enzymes; 6) enzymes bound by either reversible or irreversible exogenous inhibitors; and 7) enzymes requiring a cofactor for activity. The enzymes of interest will usually have at least one of serine, threonine, cysteine, histidine, lysine, arginine, aspartate or glutamate as a member of the active site involved in the catalysis of the enzyme reaction. One or more of the functionalities of these amino acids may be the target of the ABP. The manner in which the inactive enzyme is inactivated is chosen to emphasize the differences in bonding of the ABP between the active and inactive state.

For all of the reasons set forth above, it is respectfully submitted that the rejection of claims 12, 14, 16-18, and 20-24 under 35 U.S.C. § 112, first paragraph, as allegedly

lacking an enabling disclosure, is not properly applied. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

E. Rejection Under 35 U.S.C. 102(b)

The rejection of claims 12, 14, 16, and 20-21 under 35 U.S.C. 102(b), as allegedly being anticipated by Purohit et al. (*Biochemistry*, 1995, *34*, 11508-11514). The present invention, as defined for example by claim 12, requires a method for screening for molecules having an affinity for an active protein in a complex mixture of proteins from a biological source, employing a combinatorial chemical library comprising a plurality of members of the formula

R* (F – L) – X

wherein:

X is a ligand having the same chemical structure for each of said members of said combinatorial chemical library,

L is a bond or alkylene or an alkyleneoxy chain linking group of from 1 to 6 alkyleneoxy groups, wherein said alkyleneoxy groups are of from 2 to 3 carbon atoms, which is the same in each of the members of said combinatorial chemical library;

F is a sulfonyl functional group reactive at an active site of a protein member, which functional group comprises the same reactive functionality in each of the members of said combinatorial chemical library, and

R is a group of less than 1kDal, that is different in each of the members of the combinatorial chemical library;

the * intends that R is a part of F or L; and

wherein members of said combinatorial chemical library have different on rates with said protein member; said method comprising:

(1) combining with said complex mixture of proteins, in an active form and an inactivated form, said combinatorial chemical library under conditions for reaction of said sulfonyl functional group with active proteins to form a conjugate;

(2) isolating conjugates from said active and inactivated complex mixture of proteins; and

(3) comparing conjugates formed with said active and inactivated complex mixtures of proteins;

whereby conjugates in said active complex mixture absent in said inactivated complex mixture are comprised only of active proteins reactive with members of said chemical combinatorial library.

Purohit et al. does not describe such a method. Instead, Purohit merely describes inhibition of a particular protein, steroid sulfatase. The present invention is not drawn to simple protein inhibition. Instead, the present invention offers the ability to profile classes of proteins in a sample on the basis of changes in protein activity rather than simply variations in protein level. In contrast to the present invention, the methods described in Purohit are not able to differeniate a complex mixture of proteins on the basis of activity.

Purohit clearly does not meet all the requirements of the present invention. Accordingly, reconsideration and withdrawal of the rejection of claims 12, 14, 16, 20, and 21 under 35 U.S.C. 102(b) are respectfully requested.

C. Rejection Under 35 U.S.C. § 103(a)

The rejection of claims 12, 14, 16-18, and 20-24 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Gygi et al. (*Nature Biotechnology* , 1999, 17(10):994-999), Liu et al. (*PNAS*, 1999, 96(26):14694-14699), and Bogyo et al. (*PNAS*, 1996, 94, 6629-6634), is respectfully traversed. None of the cited references, either alone or in combination, disclose or suggest the methods of the present invention.

Applicants' invention, as defined for example, by claim 12, distinguishes over each of the cited references by requiring a method for screening for molecules having an

affinity for an active protein in a complex mixture of proteins from a biological source, employing a combinatorial chemical library comprising a plurality of members of the formula

$$R^* (F - L) - X$$

wherein:

X is a ligand having the same chemical structure for each of said members of said combinatorial chemical library,

L is a bond or alkylene or an alkyleneoxy chain linking group of from 1 to 6 alkyleneoxy groups, wherein said alkyleneoxy groups are of from 2 to 3 carbon atoms, which is the same in each of the members of said combinatorial chemical library;

F is a sulfonyl functional group reactive at an active site of a protein member, which functional group comprises the same reactive functionality in each of the members of said combinatorial chemical library, and

R is a group of less than 1kDal, that is different in each of the members of the combinatorial chemical library;

the * intends that R is a part of F or L; and

wherein members of said combinatorial chemical library have different on rates with said protein member; said method comprising:

(1) combining with said complex mixture of proteins, in an active form and an inactivated form, said combinatorial chemical library under conditions for reaction of said sulfonyl functional group with active proteins to form a conjugate;

(2) isolating conjugates from said active and inactivated complex mixture of proteins; and

(3) comparing conjugates formed with said active and inactivated complex mixtures of proteins;

whereby conjugates in said active complex mixture absent in said inactivated complex mixture are comprised only of active proteins reactive with members of said chemical combinatorial library.

The present invention describes screening methods employing probes that are able to record variations in protein activity, rather than merely level of protein expressed in a cell. Gygi et al. is silent with respect to screening methods employing probes that are able to record variations in protein activity. Indeed, it is submitted that Gygi et al. can not record variations in protein activity since Gygi et al. does not employ the well-defined, activity based probes set forth in the present invention. Instead, Gygi et al. merely describes a method for quantifying individual proteins in a mixture, regardless of the level of protein activity in the mixture. In addition, the protein mixture described in Gygi is denatured, wherein all protein structure and activity has been destroyed. Thus, Gygi's probes react with all available reaction sites on all proteins in the mixture. In contrast, the probes set forth in the present invention react with an active site of a protein. Accordingly, it is respectfully submitted that Gygi et al. does not disclose or suggest the methods of the present invention.

Moreover, Applicants respectfully submit that Liu is not available as prior art under 35 U.S.C. 103(a) since the subject matter set forth in Liu was derived from Applicants' own work. Indeed, it is noted present inventors Cravatt and Patricelli are co-authors of the Liu publication, and as set forth in the declaration filed in co-pending Application No. 09/738,954 (attached herewith as Exhibit A), Liu did not contribute to the mental conception of the present invention. Thus, it is submitted that Liu is not properly combined with either Gygi or Bogyo in a rejection under 35 U.S.C. 103(a). Accordingly, reconsideration and withdrawal of the rejection of claims 12, 14, 16-18, and 20-24 are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved, the Examiner is requested to contact the undersigned at the telephone number given below so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: 1/8/04

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